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10/530,217	03/30/2005	Yusuke Nakamura	082368-003910US	1888

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Docket@Townsend.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,217	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,19,22 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8,19,22 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/28/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/10/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed 3/28/08, Claims 8, 19, 22, and 33 are pending and examined herein.

Priority---reiterated

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/414,867, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112

for one or more claims of this application. Specifically, Application No. 60/414,867 does not provide adequate written description support for claims to small interfering RNAs against polynucleotides encoding polypeptide SEQ ID NO:16. While Application No. 60/414,867 contemplates using antisense oligonucleotides against any of a number of upregulated genes disclosed therein, including the sequence encoding hypothetical protein FLJ22357 (see Table 3 therein), the dislcosure does not explicitly or clearly comprehend siRNAs against FLJ22357.

Additionally, and more specifically, Application No. 60/414,867 does not describe an siRNA comprising or consisting of instantly claimed SEQ ID NO:13, or methods of use thereof.

Furthermore, Application No. 60/414,867 does not provide adequate enabling support for the use of compositions comprising siRNAs such as instant SEQ ID NO:13 against polynucleotides encoding polypeptide SEQ ID NO:16 to treat any proliferative disease such as cancer.

For purposes of this examination, the earliest effective filing date of claims 8, 19, 22, and 33 is considered to be that of PCT/JP03/09589: 7/29/2003.

In the reply filed 3/28/08, Applicant does not traverse the finding.

Claim Objections

Claim 8 is objected to because of a minor inormality. Line 4 recites "a polypeptide comprises the amino acid sequence of SEQ ID NO:16." The wording "comprising" or "that comprises" would be preferable.

***

Claim 10 is objected to because it does not comply with 37 CFR 1.121(c)(4)(i), stating that no text shall be presented for a claim listed as cancelled.

Specification/Sequence Compliance

The disclosure is objected to because of the following: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

In particular, the amino acid sequence set forth in Fig. 1b are not accompanied by SEQ ID NO: identifiers.

This is but a sampling of the many sequences set forth in the instant application. Applicants are advised to review the entire application—claims, drawings, and specification—for complete compliance with the Sequence Rules.

Thus, the Examiner notes herein that the above listing of figures which set forth examples in the specification of nucleotide and/or amino acid sequences that require SEQ ID NO: is by way of illustration. In order to be fully responsive to this Office Action, Applicant should review this application in its entirety to ensure compliance with the requirements of 37 CFR 1.821 through 1.825 and to make all appropriate corrections.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Requirement for Information under 37 CFR 1.105

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

Based on disclosure at page 24 of the specification, the examiner has reason to believe, that a publicly available, online computer algorithm based on known relevant physical properties for short interfering RNAs may have been used to identify the claimed siRNA, comprising or consisting of SEQ ID NO:13. The Ambion online siRNA design tool (www.ambion.com) available as of the date of this Action recommends an siRNA comprising SEQ ID NO:13 for inhibition of the mRNA corresponding to GenBank Acc. No. NM_022450---Homo sapiens rhomboid 5 homolog 1 (RHBDF1), the gene said to be targeted by instant SEQ ID NO:13 (see page 40 of the specification).

In response to this requirement, please identify any algorithms used to identify the claimed siRNA. If there are publications, including web-based disclosures, directed to describing this algorithm, the title, citation and copy of any such publications should also be provided. It may be appropriate to supply such references in an information disclosure statement. See below for waiver of certain requirements of 37 CFR 1.97. For each publication, please provide a concise explanation of the reliance placed on that publication in the development of the disclosed subject matter.

The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

/JD Schultz, PhD/

Supervisory Patent Examiner, Art Unit 1635

Claim Rejections - 35 USC § 103

Claims 8, 19, 22, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arts et al. (WO 2004/094636 A1) in view of Tuschl et al. (US 2004/0259247 A1), Bass (2001) *Nature* 411:428-429, and Fosnaugh et al. (US 2003/0143732 A1).

Claim interpretation:

Firstly, Claims 19, 22, and 33 contain language describing intended uses of the claimed compositions. For example, the claims recite compositions "for treating a cell proliferative disease" such as "leukemia or lung cancer." These recitations add little if any patentable weight to the instant claims (MPEP 2111.02). In the instant case, the body of the claims fully and intrinsically set forth all of the limitations of the claimed invention. Accordingly, the preamble is not considered a limitation and is of no significance to claim construction. A disclosure or suggestion in the prior art to make the composition defined in the body of the claim for any reason is sufficient to defeat patentability. The intended uses breath life and meaning into the claims only to the extent the compositions must comprise "a pharmaceutically acceptable amount" of the claimed siRNA. The amount would reasonably be one suitable for the intended use. However, neither the claims nor the specification explicitly define "a pharmaceutically acceptable amount" in a manner that would enable one of skill to distinguish the claimed compositions from those disclosed and suggested by the prior art. Accordingly, the limitation "a pharmaceutically acceptable amount" is construed very broadly to include virtually any concentration or amount. Even if the amount were defined it is not clear this would render the claimed compositions patentable since the formulation and preparation of pharmaceutical

compositions comprising siRNA for a broad variety of intended uses was well known in the prior art, as evidenced by Fosnaugh et al., for example.

Secondly, while the claims have been amended to recite "wherein the sense strand consists of," the claims include the phrase "corresponding to." The scope and meaning of this phrase, corresponding to, is not explicitly defined by the specification or the claims. In fact, the specification is most clearly directed to siRNAs comprising SEQ ID NO:13. Thus, the limitation "consists of" following by the limitation "corresponding to" renders the metes and bounds of the claims somewhat unclear, inasmuch as narrow limitation is followed by a broad limitation which includes sense strands consisting of SEQ ID NO:13, but also corresponding to SEQ ID NO:13, which may reasonably include 21-mers comprising SEQ ID NO:13. Accordingly, because of the "corresponding to" language, the claims continue to embrace siRNAs comprising 21-nt sense strands comprising SEQ ID NO:13 as well as siRNAs having sense strands consisting of SEQ ID NO:13. Both interpretations are addressed by the following rejection.

The rejection:

Arts et al. (WO 2004/094636 A1) in view of Tuschl et al. (US 2004/0259247 A1) and Fosnaugh et al. (US 2003/0143732 A1) suggested an siRNA comprising a sense strand consisting of SEQ ID NO:13, as follows.

Arts et al. disclosed a short interfering RNA comprising instant SEQ ID NO:13 for the inhibition of the gene corresponding to GenBank Accession No. NM_022450, encoding protein FLJ22357. See SEQ ID NO:8317 in Table 1, page 290. Image provided below.

Compare instant SEQ ID NO: 13 (gtacgtgcagcaggagaac) to SEQ ID NO:8317.

Polypeptide FLJ22357 is identical to instantly recited SEQ ID NO:16.

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NM_022450	FLJ22357	8316	ACTGGCAGCGCAAGAGCATCC
NM_022450	FLJ22357	8317	ACGTACGTGCAGCAGGAGAAC
NM_022450	FLJ22357	8318	ACCCTGGCCAGTGCCATCTTC

To the extent that Arts et al. taught that these siRNAs can be used to inhibit this target gene, and in view of the wealth of technical guidance and direction in the RNAi art at the time of invention, as evidenced by Tuschl et al. and Fosnaugh et al., the disclosure is enabling since one of skill could make and use the siRNA in the manner intended. The references need not prove the operability of the siRNA to qualify as prior art. A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). In the instant case, in view of the level of skill and knowledge in the RNAi art at the time of invention, the Examiner finds no evidence one of skill would be required to engage in undue experimentation to make and use the claimed siRNA or compositions thereof (MPEP 2121.01) for use in vitro. Applicant will note that the compositions of claims 19, 22, and 33 are not limited to in vivo use. The compositions may be disclosed by the prior art even if for a purpose different from that intended by applicant, so long as the prior art discloses the composition with all its claimed limitations.

While Arts et al. do not teach an siRNA comprising a sense strand consisting of SEQ ID NO:13, Arts et al. make it clear that each of positions 3-21 of the 21-nucleotide siRNAs disclosed therein represent the 19-nucleotide target/guide sequence and that each siRNA/target site sequence should be preceded by an "AC" dinucleotide. See pages 4-6. Thus, one of skill would recognize that the site targeted by siRNA 8317 specifically corresponds to positions 3-21 of siRNA 8317. Thus, one of skill would have immediately envisioned the 19-nt sense strand corresponding to siRNA 8317.

Tuschl et al. taught methods and materials for making and using siRNAs to inhibit the expression of virtually any known gene in vitro and in vivo for research and therapeutic purposes. Tuschl et al. taught that siRNAs may be formulated as pharmaceutical compositions containing as active ingredient at least one double stranded RNA and a pharmaceutical carrier (paragraph 32). It is said the composition may be used for diagnostic as well as therapeutic purposes (paragraph 32 and 33). Tuschl et al. taught that the sense and antisense strands of an siRNA may be 19, 20, 21, 22, or 23 nucleotides in length (Fig. 12 and see discussion at paragraph 162). Various combinations thereof are all shown to have RNAi activity (Fig. 12). Accordingly, it was known in the prior art that an siRNA may be of any length between 19 and 21-nucleotides.

Fosnaugh et al. supplements Tuschl et al. teaching methods and materials for making pharmaceutical compositions comprising siRNA (pp. 23-26).

Accordingly, the siRNA comprising a sense strand consisting of instant SEQ ID NO:13 would have been prima facie obvious to one of skill at the time of invention. One of skill would have had reason to make and use the instantly claimed siRNA given that Arts et al. explicitly

state that an siRNA comprising SEQ ID NO:13 may be used to inhibit the cited target gene; given that Tuschl et al. showed that siRNAs comprising sense and antisense strands of various lengths may be used to inhibit gene expression, albeit with different relative activities, and given that it would have been the normal desire of the scientist to optimize the activity, stability, and uptake of the siRNA, by, for example, altering the relative lengths of the sense and antisense strands.

It is the normal desire of scientists to understand the function of every expressed protein in every cell in every species. At the time of invention, siRNAs were universally recognized, art-accepted tools for probing gene function, using classical loss-of-function analyses (reverse genetics) to identify phenotypes associated with any given protein. For example, Tuschl et al. taught the materials and methods for making and using siRNAs against virtually any known sequence for both research and therapeutic purposes in cells in vitro and in vivo. See entire specification, especially pages 1-7. As such Tuschl et al. represents a complete blueprint for the design and synthesis of siRNAs and application of RNAi technology for inhibiting gene expression in any mammalian cell. At paragraph 29 therein, Tuschl et al. taught that the method [RNAi] may be used for determining the function of a gene in a cell or an organism. At paragraph 30, it is said that by inhibiting the function of a gene valuable information and therapeutic benefits in the agricultural field or in the medicine or veterinary medicine field may be obtained.

Bass also taught the advantages of RNAi for gene function research, stating that "Once the sequence of a gene is known, RNAi offers a quick and easy way to determine its function,

and the technique is accessible to a scientist in a small lab, as well as to a consortium attempting to assign function to the genes of an entire chromosome" (page 428, left column).

Accordingly, one of skill in the art would have considered it obvious at the time of invention to make and use siRNAs to any known gene, including the siRNA suggested by Arts et al., as a tool to investigate and/or further characterize the function of the gene said to be inhibited by the siRNA taught by Arts et al. Knockdown is but one type of investigative tool the skilled practitioner would turn to during the course of any study designed to determine the biological function of a gene. At the time, RNAi was known to be readily accessible and highly potent method for knocking down the expression of a gene and thereby for probing the essential or non-essential nature of gene.

Thus, the use of RNAi as a tool to determine gene function is suggested and taught by the prior art (Tuschl et al. and Bass, for example). Therefore, for all these reasons, one of skill would have been both well motivated and have had reasonable expectation of success in making and using the siRNA suggested by Arts et al. Given that it is the normal desire of scientists to improve upon what is already known in the prior art, the practitioner would reasonably have been expected to engage in routine experimentation to optimize the activity of siRNA 8317 of Arts et al., which Tuschl et al. taught may be influenced by the length of either the sense or antisense strand or both.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 19, 22, and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendment to the claims submitted on 3/28/2008, introduces the limitation "wherein the sense strand thereof consists of a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO:13" into independent claims 8 and 19.

MPEP 2163, Section II, Part A, states in part that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims.

The purpose of the written description requirement is "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." MPEP 2138.05, I.

In the instant case, Applicant points to original claim 10 and "throughout the specification" as support for the new amendment limiting the claims to an siRNA wherein the sense strand consists of SEQ ID NO:13. As stated by MPEP 2111.03, the transitional phrase

"consisting of" excludes any element, step, or ingredient not specified in the claim. Thus, the clear intention of the amendment is to limit the claims to an siRNA wherein the sense strand is no longer than SEQ ID NO:13, a 19-nt sequence. Previously, the claims embraced siRNAs comprising SEQ ID NO:13.

However, neither original claim 10 nor the specification as a whole provides support for the siRNA as now claimed, which is now limited to siRNAs wherein the antisense strand may be, for example, 19-23 nucleotides in length, but the sense strand is precisely 19 nucleotides in length and consists of SEQ ID NO:13. No such siRNAs are explicitly or implicitly disclosed in the instant application. Rather, it is clear the instant application contemplates using conventional 21-nucleotide siRNAs and shRNAs comprising SEQ ID NO:13. Thus, the application provides written description support for siRNAs comprising 21-nucleotide sense strands comprising SEQ ID NO:13 and 2-nucleotide overhangs.

Original claim 10 uses open-ended, comprising, not consisting of language. Design principles described at page 24 of the specification are directed to the selection of 21-mers, and there is no disclosure indicating or suggesting use of paired s/as strands in the form 19-nt/19-nt or 19-nt/21-nt; rather, the disclosure relies on the art-accepted meaning of the term "siRNA", which in common practice typically refers to 21-nt/21-nt duplexes with 3'-nt overhangs. Statements therein describing SEQ ID NO:13 as a target sequence in RHBDF1 (page 41 for example) are consistent with this interpretation. Obviousness cannot be relied on for written description support, what is needed is explicit, implicit, or inherent support for the invention as claimed. No such support is currently found.

Accordingly, the instant claims as a whole are rejected for lack of written description support because one of skill in the art would not have immediately envisioned the invention as now claimed from the disclosure as originally filed.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)

Claims 19 and 22 remain rejected and new claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to siRNA-containing compositions for treating a cell proliferative disease, such as cancer, including leukemia and lung cancer.

The "pharmaceutically effective amount" and "pharmaceutically acceptable carrier" language in combination with the intended use recited in the preamble for treating a cell proliferative disease requires that these claims be evaluated to determine whether the specification teaches how to use these compositions for treating any proliferative disease, particularly cancer.

Neither the specification nor the prior art provide adequate representation of the claimed use for treating proliferative disease in vivo using the claimed composition. While the specification shows inhibition of the target gene in K562 cells in vitro slows cell growth, and expression of the target gene enhances cell growth in an immortalized cell line, these data are not readily extrapolated to treatments of proliferative disease in vivo. The data merely show that the gene may be required for cell division, not that it is an oncogene per se. Cancer is a multifactorial process. More would be required before one of skill in the art would be able to use the claimed compositions in the manner intended to selectively treat abnormal cell division in vivo. Many genes are involved in cell division. While overexpression of the instant gene may spur cell growth, many genes when overexpressed may alter cell division. Similarly, many different genes when underexpressed may slow cell growth. A nexus has not been established reasonably linking the target gene with proliferative disease in a living organism. No evidence, direct or indirect, has been provided to lead one of skill in the art to believe that providing the claimed composition to a mammal affected proliferative disease would provide a treatment effect, wherein the diseased cells are selectively targeted and inhibited.

Additionally, problems related to the pharmaceutical use of siRNAs and antisense nucleic acids were well known in the art at the time of invention. Such problems include the inability to

routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Hannon and Rossi (2004) *Nature* 431:371–378 teach that, while RNAi has the potential to be exploited therapeutically, and despite early proofs of principle, "there are important issues and concerns about the therapeutic application of this technology, including difficulties with delivery and uncertainty about potential toxicity." (page 374, 2nd column) "Two key challenges in developing RNAi as a therapy are avoiding off-target effects and ensuring efficient delivery." (page 377, 1st column) "The issue of delivery has restricted the antisense field for almost two decades. It is feasible to infuse backbone-modified oligonucleotides *in vivo*, but achieving intracellular delivery at therapeutically effective concentrations is a major challenge. Targeted delivery to specific cell or tissue types is still not a practical reality for oligonucleotide-based therapeutics." (page 377, 2nd column) "As with HIV therapeutics, delivery of the siRNAs or shRNA vectors is the main challenge for successful treatment of HCV. The method of delivery used in several *in vivo* studies—hydrodynamic intravenous injection—is not feasible for the treatment of human hepatitis." (page 376) "However, enhancing siRNA stability is not enough unless the siRNAs can penetrate cells and tissue *in vivo* in concentrations sufficient to be therapeutically functional. As siRNAs are double-stranded molecules, delivery and cellular uptake is more of a challenge than for single-stranded antisense agents, which bind to serum proteins and are taken up by cells and tissues *in vivo*. There are a few reports of functional RNAi being obtained by systemic delivery of liposome-encapsulated siRNAs,…" (page 376) "Systemic delivery of siRNAs to T lymphocytes is probably not feasible owing to the immense number of these cells. Using viral vectors to deliver anti-HIV-encoding shRNA genes is also problematic,

and systemic delivery is not yet practicable because the immunogenicity of the vectors themselves precludes performing multiple injections." (page 375)

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

A review of the instant application fails to find exemplary disclosure illustrating the proposed use of the compositions to treat cell proliferative diseases in any organism, mammal, or human subject. Instead, the specification makes general assertions that one of skill in the art would know how to apply (dose, frequency, and duration) the antisense oligos to the lungs (pages 32-34, for example). Examples of in vivo use of the pharmaceutical compositions, working or otherwise, are not provided.

Cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides to cells in any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in*

vitro, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the “for treating a cell proliferative disease,” "wherein the cell proliferative disease is cancer," and "wherein the cell proliferative disease is chronic myeloid leukemia or lung cancer" language from the instant claims would overcome this rejection. The rejection is not to the compositions per se but to the intended use and characterization of the compositions as pharmaceutical compositions when, in fact, the neither the specification nor the prior art enables at least one pharmaceutical use for treating a cell proliferative disease, nor offers assurance that one of skill could use the claimed compositions in the manner intended without engaging in undue experimentation.

Response to Arguments

Applicant's arguments traversing and requesting withdrawal of the instant rejection for lack of enablement have been fully considered but are not persuasive. MPEP 2164.01(c) states that when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Following this guidance, the specification must teach how to use the composition to treat at least one cell proliferative disease, at least one cancer, at least one chronic myeloid leukemia, and at least one lung cancer, or any art-recognized equivalent thereof. While "treatment" per se does not carry a particularly high bar, in light of the explicit statements in the claims that the compositions may be used to treat cancer it is reasonable to question whether the specification enables one of skill to use the claimed compositions to alleviate or otherwise positively influence the progression or outcome of a cell proliferative disease, cancer, leukemia, or lung cancer in a patient suffering from said disease without having to engage in undue experimentation. That is, it is reasonable to question whether sufficient guidance and direction are present to enable one of skill to use the claimed compositions in the manner intended.

Applicant's points are well taken. However, examples of in vitro use in select, model cell lines are not considered to be generally representative of an in vivo use to treat any patient having, for example, lung cancer or leukemia. Aside from Applicants blanket assertion, there is absolutely no objective evidence these in vitro examples could be reasonably extrapolated to any in vivo use, apart from the inhibition of the same gene in vivo. While it is clear that one of skill could reasonably use the claimed compositions in vivo to inhibit the expression of the target

gene in vivo without having to engage in undue experimentation, there is insufficient evidence and a general lack of enabling disclosure in the prior art to show the inhibition of the gene in vivo would positively affect the outcome or progression of any cancer: no reasonable nexus has been established between reduced expression of the target gene in vivo and the treatment of any cell proliferative disease, much less leukemia or lung cancer.

It is true, gene therapy is an inherently unpredictable field, wherein success or failure depend on many different factors, including the ability to deliver the nucleic acid into the target cells in an amount sufficient to produce a treatment effect. However, the Examiner fully acknowledges practitioners in this field are required to engage in this type of experimentation regularly; thus, this experimentation is not by itself considered undue. Nevertheless, when these challenges are considered together with the complete absence of any evidence showing or even suggesting that inhibition of RHBDF1 in a subject may be used to treat lung cancer or leukemia, it becomes an important contributing factor. The finding that cells genetically manipulated to overexpress a gene such as RHBDF1 behave abnormally, and that reducing overexpression with a nucleic acid antisense or siRNA reverses or subdues this trend, is not representative of the claimed use of treating a cancer in vivo; rather it represents a starting point for future research regarding the role RHBDF1 may play in cancer in vivo.

Applicant cites MPEP passages and case law regarding utility; however, the rejection is not for lack of utility but for lack of disclosure enabling at least one therapeutic use in vivo to treat a cancer. The Office is not requiring clinical data, or even direct proof, but simply disclosure in the specification, prior or post-filing art, reasonably correlating the reduction or inhibition of RHBDF1 (protein activity or gene expression) in vivo and treatment of lung cancer

or leukemia, each of which may be triggered and spurred on by multiple different genetic lesions or defects. Any evidence with any type of inhibitor (small or large molecule, antibody, peptide, or nucleic acid) showing that the inhibition of the RHBDF1 protein or gene encoding said protein provides for a treatment effect would suffice. However, Applicant cites no evidence but only argues the impropriety of the rejection.

The rejection is maintained therefore for the reasons earlier stated, as reiterated and amplified above.

Art made of record but not currently relied on

The following art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure.

Nakamura et al. (US 2006/0210576 A1), though now abandoned, would be considered pertinent to the instant claims if revived inasmuch as Nakumura et al. contained claims, claims 15-17, to a composition for treating a metastatic lesion of colorectal cancer or preventing metastasis of colorectal cancer in a subject, comprising a pharmaceutically effective amount of a small interference RNA against one or more genes selected from the group consisting of MLXs 1-153. MLX 44, disclosed in Table 1 at page 1 of the specification, corresponds to hypothetical protein FLJ22357, identical to instant nucleic acid SEQ ID NO:15.

Response to Applicants' Arguments

Applicants' arguments presented on 3/28/08 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Examiner, Art Unit 1635
June 20, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635